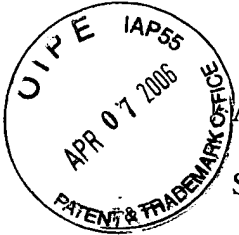


PATENT
Attorney Docket No. 3309

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES**



Applicants: Daniel M. Bartell, et al.

Examiner: Marschel, Ardin H

Serial No: 09/737,536

Group Art Unit: 1631

Filing Date: Dec. 13, 2000

Title: **SYSTEMS AND COMPUTER
SOFTWARE PRODUCTS FOR
COMPARING MICROARRAY SPOT
INTENSITIES**

APPEAL BRIEF

Commissioner for Patents
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APPEAL BRIEF**I. Introduction**

This is an appeal from the final rejection of the examiner dated March 09, 2005 and Advisory Action of October 11, 2005. This brief is accompanied by the requisite fees set forth in 37 C.F.R. § 41.20(b)(2).

II. Real Party in Interest

The real party in interest in this application is Affymetrix, Inc.

III. Related Appeals and Interferences

There are no related appeals or interferences material to this application.

IV. Status of the Claims

Claims 1-31 are pending and the subject of this appeal. Claims 32-52 have been cancelled.

V. Status of Amendments

Applicants amendment to the claims (1-31) filed December 08, 2004 are deemed to be entered. No amendments to these claims were filed after the mailing of the after the mailing of the final Office Action on March 9, 2005. The claims 1-31 set forth in the Appendix include the amendments set forth in all amendments.

VI. Summary of the Claimed Subject Matter

Recent technologies utilize microarray data analysis in for example detecting the presence of RNA transcripts, analyze the gene expression profile, monitoring, genotyping and other polymorphism analysis, diagnosis, etc. Microarrays are useful for many practical applications such as drug discovery and clinical diagnostics.

An embodiment of the invention provides with methods for comparing a first microarray spot with a second microarray spot wherein the methods include the steps of: providing a first plurality of hybridization intensity values for the first microarray spot and a second plurality of hybridization intensity values for a second microarray spot;

calculating a p value using Wilcoxon's rank test to identify the difference of intensities between the first and the second plurality of hybridization intensity values; and indicating that the first microarray spot is different from the second microarray spot if the p value is greater than a significance level (see for example paragraph beginning on page 3 line 19).

In another aspect of the invention, the first microarray spot and second microarray spot may be nucleic acid spots among at least 10, 50, 100, 200, 400, 500, 750, 1,000, 5,000, 10,000, 20,000, 30,000 or more nucleic acid spots on a substrate. Exemplary nucleic acid spots include cDNA spots or oligonucleotide spots (either synthesized on the substrate or spotted). In some embodiments, the methods may include combining first plurality and second plurality of intensity values if the p -value is greater than a significance level, such as $p > 0.5$.

In other embodiments of the invention provide for computer software products and systems for comparing a first plurality hybridization intensity values for a first microarray spot with a second plurality of hybridization intensity values for a second microarray spot wherein a p value is calculated using a Wilcoxon's rank test to indicate the difference between the first microarray spot and the second microarray spot. (see for example page 4, lines 13-22 and page 5, lines 11-21).

VII. Grounds of Rejections to be Reviewed on Appeal

- A. Claims 1-31 are rejected under 35 USC 112, first paragraph, as allegedly failing to comply with the enablement requirement.
- B. Claims 1-31 are also rejected under 35 USC 101 as allegedly being directed to non-statutory subject matter.

VIII. Argument

- A. **The claims meet the Enablement Requirement of 35 U.S.C. 112, first paragraph, that the specification enable any person skilled in the art to make and use the invention.**

The Examiner alleges that the calculation of p value is an essential subject matter and therefore, it is inappropriate to provide support using incorporated materials. Calculation and evaluation of p value for a Wilcoxon rank test is well known to one of skill in the art. The theory and practice of Wilcoxon's rank test are described in numerous textbooks, including those that are incorporated by reference in the specification. In addition, the specification provides sufficient directions and specific examples. A patent need not teach, and preferably omits, what is well known in the art. Therefore, Applicants respectfully submit that an amendment to include the material incorporated by reference is not needed. This rejection under 35 USC 112 should be withdrawn.

The Examiner alleges that the calculation of p value and the theory and practice of Wilcoxon's rank test is not well known in the art and not factually supported in the specification. Applicants respectfully disagree. It is well known to one of ordinary skill in statistics that p-value represents a probability value. The probability value (p value) of a statistical hypothesis test is the probability of getting a value of the test statistic as extreme as or more extreme than that observed by chance alone, if the null hypothesis H_0 , is true. In other words, it is the probability of wrongly rejecting the null hypothesis if it is in fact true. Additionally, Wilcoxon's Rank Sum Test is well known to one of ordinary skill in statistics. The Wilcoxon's Rank Sum Test was first proposed by Frank Wilcoxon in 1945 (Wilcoxon, F. (1945) "Individual Comparisons by Ranking Methods," *Biometrics* 1, 80-83). It has since been widely used as a nonparametric statistics to compare two independent samples of observations. Like other statistical comparison methods, the method Wilcoxon developed is to calculate the p value for evaluation. Therefore, methods for calculating p value for a Wilcoxon rank test had been known as early as 1945. Applicants also wish to point out that once a p value is calculated according to Wilcoxon, it was also well known to one of ordinary skill in the art that the threshold value for the p value to call significance is dependent upon the tester's purpose and preferences. It was also well known that the significance levels are often set at $p=0.05$ (significant) or $p=0.01$ (very significant). Such basic statistic principles and methods are taught in numerous statistic textbooks such as those cited in the specification. Therefore, Applicants respectfully submit that an amendment to include

the material incorporated by reference is not needed. This rejection under 35 U.S.C. § 112 should be withdrawn.

B. The claims meet the requirement of 35 U.S.C. 101, that the claimed invention be directed to statutory subject matter.

Claims 1-31 have been rejected as allegedly being directed to a non-statutory subject matter. The Office Action asserts that the claims are drawn to computation without any physical process and point to the “Computer-Related Inventions” section of the MPEP, Part IV, Subpart B.

Applicants respectfully disagree. In *State Street Bank & Trust Co. v. Signature Fin. Group, Inc.*, 149 F.3d 1368, 1374,-75, the Fed Cir. concluded that “Unpatentable mathematical algorithms are identifiable by showing they are merely abstract ideas constituting disembodied concepts or truths that are not ‘useful’.” In *State Street Bank*, the Fed Cir. held that “the transformation of data, representing discrete dollar amounts, by a machine through a series of mathematical calculations into a final share price, constitutes a practical application of a mathematical algorithm, formula, or calculation, because it produces “a useful, concrete and tangible result”--a final share price momentarily fixed for recording and reporting purposes and even accepted and relied upon by regulatory authorities and in subsequent trades.”

In *ATT Corp. v. Excel Comm. Co.*, 172 F.3d 1352, 1361, further clarified the issue of mathematical algorithm exception by concluding that “[t]he *State Street Bank* formulation, that **a mathematical algorithm may be an integral part of patentable subject matter such as a machine or a process if the claimed invention as a whole is applied in a “useful” manner....[emphasis added]**” The Fed. Cir. also held that patent claims reciting method of indicating telephone call recipient’s primary interexchange carrier as data field was a patentable subject matter, as process applying Boolean principle to produce useful, concrete and tangible result.

Applying the *State Street* and its progenies to the rejected claims, Applicants respectfully submit that the instant claims are directed to the comparison of two microarray spot intensities. As stated in the Specification, the comparison of probe intensities at each cDNA target location is an important part of microarray data analysis

such as analysis of gene expression profile (Page 21, lines 13-22 and Abstract). The claimed process produces concrete and useful results.

Microarray data analysis produces scientifically important results such as detecting the presence of RNA transcripts (Summary, Page 6, lines 10-12). Microarrays have been used for many practical applications such as drug discovery and clinical diagnostics. Microarray data analysis could be useful in gene expression monitoring, genotyping and other polymorphism analysis, diagnostics, etc. (Page 35, lines 11-12).

The Office Action alleges that “the instant claims are directed to non-statutory subject matter without requiring performance of a result outside of a computer type computation. Thus, the manipulation of data or conversion of data, in this case intensity values, is the claimed subject matter without any physical transformation beyond that of a computation.” Office Action, page 5. Applicants respectfully submit that the Fed Cir. in *ATT Corp.* specifically rejected physical transformation as an invariable requirement and held that patent claims containing mathematical algorithms need not involve physical transformation to be deemed patentable subject matter: “the notation of “physical transformation” can be misunderstood. In the first place, it is not an invariable requirement, but merely one example of how a mathematical algorithm may bring about a useful application.” *ATT Corp.*, 173F.3d 1358.

Therefore, because the rejected claims are directed to a process that produces useful, concrete and tangible result in the microarray and biotechnology field and thus are directed to a patentable subject matter, this rejection of Claims under 35 USC 101 should be withdrawn.

The Examiner alleges in the State Street case, that monetary transfers are useful, concrete, and tangible while in the *ATT Corp* case, a primary interexchange carrier is useful, concrete, and tangible. Applicants respectfully submit that the instant claims are directed to the comparison of two microarray spot intensities (Page 21, lines 13-22 and Abstract) which is useful, concrete, and tangible in the microarray industry. Therefore,

Applicants respectfully request that the rejection of claims under 35 U.S.C. § 101 be withdrawn.

IX. Claims Appendix

A listing of the claims which are the subject of this appeal are set forth below. The claims herein include all amendments.

X. Conclusion

For these reasons, Applicants believe all claims are in condition for allowance. If the Examiner has any questions pertaining to this application or feels that a telephone conference would in any way expedite the prosecution of the application, please do not hesitate to call the undersigned at (408) 731-5000.

The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account 01-0431.

Applicants respectfully request that a timely Notice of Allowance be issued in this case.

Respectfully submitted,

By Wei Zhou Block Reg. 50,167 for
Wei Zhou Reg. 44,419

Attachment – Claims Appendix

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CLAIMS APPENDIX

The following are the claims on appeal:

1. (previously presented) A method for comparing a first microarray spot A with a second microarray spot B comprising:
providing a first plurality of intensity values (S_i^A) for a first microarray spot A and a second plurality of intensity values (S_k^B) for a second microarray spot B, wherein i denotes a i th pixel for spot A and k denotes a k th pixel for spot B and wherein the intensity values indicate nucleic acid hybridization;
calculating a p value using Wilcoxon's rank test, wherein p value is for a null hypothesis that $\theta=0$ and an alternative hypothesis that said $\theta>0$, wherein θ is a test statistic for intensity difference between said plurality and said second plurality; and
indicating said first microarray spot is different from said second microarray spot if said p value is greater than a significance level.
2. (original) The method of Claim 1 wherein said testing statistic is $median(S_i^A) - median(S_k^B)$.
3. (original) The method of Claim 2 wherein said significance level is 0.05.
4. (original) The method of Claim 1 wherein said first microarray spot and second microarray spot are nucleic acid spots.
5. (original) The method of Claim 4 wherein said nucleic acid spots are among at least 100 nucleic acid spots on a substrate.
6. (original) The method of Claim 5 wherein said nucleic acid spots are among at least 1000 spots on a substrate.
7. (original) The method of Claim 6 wherein said nucleic acid spots are cDNA spots.

8. (original) The method of Claim 7 wherein said nucleic acid spots are oligonucleotide spots.
9. (original) The method of Claim 1 further comprising step of combining first plurality and second plurality of intensity values if said p-value is greater than a significance level.
10. (previously presented) A computer software product for comparing first microarray spot A with a second microarray spot B comprising:
 - computer program code for inputting a first plurality of intensity values (S_i^A) for a first microarray spot A and a second plurality of intensity values (S_k^B) for a second microarray spot B, wherein i denotes a i th pixel for spot A and k denotes a k th pixel for spot B and wherein the intensity values indicate nucleic acid hybridization;
 - computer program code for calculating a p value using Wilcoxon's rank test, wherein p value is for a null hypothesis that $\theta=0$ and an alternative hypothesis that said $\theta>0$, wherein θ is a test statistic for intensity difference between said plurality and said second plurality;
 - computer program code for indicating said first microarray spot is different from said second microarray spot if said p value is greater than a significance level; and
 - a computer readable media for storing said computer program codes.
11. (original) The computer program product of Claim 10 wherein said testing statistic is $median(S_i^A) - median(S_k^B)$.
12. (original) The computer software product of Claim 11 wherein said significance level is 0.05.
13. (original) The computer software product of Claim 11 further comprising computer program code for accepting user's input or selection of said significance level.
14. (original) The computer software product of Claim 11 wherein said first microarray spot and second microarray spot are nucleic acid spots.

15. (original) The computer software product of Claim 14 wherein said nucleic acid spots are among at least 100 nucleic acid spots on a substrate.
16. (original) The computer software product of Claim 15 wherein said nucleic acid spots are among at least 1000 spots on a substrate.
17. (original) The computer software product of Claim 16 wherein said nucleic acid spots are cDNA spots.
18. (original) The computer software product of Claim 16 wherein said nucleic acid spots are oligonucleotide spots.
19. (previously presented) The computer software product of Claim 10 further comprising a computer program code for combining first plurality and second plurality of intensity values if said p-value is greater than a significance level.
20. (original) The computer software product of Claim 19 wherein said significance level is 0.5.
21. (previously presented) A system for comparing nucleic acid probes comprising:
 - a processor; and
 - a memory being coupled with a processor, the memory storing a plurality machine instructions that cause the processor to perform a plurality of logical steps when implemented by the processor, said logical steps including:
 - inputting a first plurality of intensity values (S_i^A) for a first microarray spot A and a second plurality of intensity values (S_k^B) for a second microarray spot B , wherein i denotes a i th pixel for spot A and k denotes a k th pixel for spot B and wherein the intensity values indicate nucleic acid hybridization;
 - calculating a p value using Wilcoxon's rank test, wherein p value is for a null hypothesis that $\theta=0$ and an alternative hypothesis that said $\theta>0$, wherein θ is a test statistic for intensity difference between said plurality and said second plurality; and
 - indicating said first microarray spot is different from said second microarray spot if said p value is greater than a significance level.

22. (original) The system of Claim 21 wherein said testing statistic is *median* (S_i^A)-*median* (S_k^B).
23. (original) The system of Claim 22 wherein said significance level is 0.05.
24. (original) The system of Claim 22 wherein said steps further comprise accepting user's input or selection of said significance level.
25. (original) The system of Claim 21 wherein said first microarray spot and second microarray spot are nucleic acid spots.
26. (original) The system of Claim 25 wherein said nucleic acid spots are among at least 100 nucleic acid spots on a substrate.
27. (original) The system of Claim 26 wherein said nucleic acid spots are among at least 1000 spots on a substrate.
28. (original) The system of Claim 27 wherein said nucleic acid spots are cDNA spots.
29. (original) The system of Claim 27 wherein said nucleic acid spots are oligonucleotide spots.
30. (original) The system of Claim 21 further comprise combining first plurality and second plurality of intensity values if said p-value is greater than a significance level.
31. (original) The system of Claim 30 wherein said significance level is 0.5.

Claims 32-52 (cancelled)

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Effective on 12/08/2004. Fees pursuant to the Consolidated Appropriations Act, 2005 (H.R. 4818). <div style="font-size: 2em; font-weight: bold; text-align: center;">FEE TRANSMITTAL</div> <div style="font-size: 1.5em; font-weight: bold; text-align: center;">for FY 2005</div> <div style="border: 1px solid black; border-radius: 50%; width: 100px; height: 100px; display: flex; align-items: center; justify-content: center; margin: 10px auto;"> <div style="writing-mode: vertical-rl; transform: rotate(180deg); font-size: 0.8em;">RECEIVED</div> <div style="text-align: center;"> <div style="font-size: 0.8em;">APR 07 2006</div> <div style="font-size: 0.8em;">U.S. PATENT & TRADEMARK OFFICE</div> </div> </div>		Complete if Known	
<input checked="" type="checkbox"/> Applicant claims small entity status. See 37 CFR 1.27		Application Number 09/737,536	Filing Date December 13, 2000
TOTAL AMOUNT OF PAYMENT (\$) 500.00		First Named Inventor Daniel M. Bartell	Examiner Name Ardin H. Marschel
		Art Unit 1631	Attorney Docket No. 3309

METHOD OF PAYMENT (check all that apply)
☐ Check ☐ Credit Card ☐ Money Order ☐ None ☐ Other (please identify) : _____

☒ Deposit Account Deposit Account Number: 01-0431 Deposit Account Name: Affymetrix, Inc.

For the above-identified deposit account, the Director is hereby authorized to: (check all that apply)

☒ Charge fee(s) indicated below ☐ Charge fee(s) indicated below, except for the filing fee

☒ Charge any additional fee(s) or underpayments of fee(s) ☐ Credit any overpayments

Under 37 CFR 1.16 and 1.17

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.
FEE CALCULATION**1. BASIC FILING, SEARCH, AND EXAMINATION FEES**

Application Type	FILING FEES		SEARCH FEES		EXAMINATION FEES		Fees Paid (\$)
	Fee (\$)	Small Entity Fee(\$)	Fee(\$)	Small Entity Fee(\$)	Fee(\$)	Small Entity Fee(\$)	
Utility	300	150	500	250	200	100	_____
Design	200	100	100	50	130	65	_____
Plant	200	100	300	150	160	80	_____
Reissue	300	150	500	250	600	300	_____
Provisional	200	100	0	0	0	0	_____

2. EXCESS CLAIM FEES**Fee Description**

Each claim over 20 (including Reissues)

Each independent claim over 3 (including Reissues)

Multiple dependent claims

Total Claims	Extra Claims	Fee(\$)	Fee Paid (\$)
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_____ -20 or HP= _____	x	_____	= _____
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HP = highest number of total claims paid for, if greater than 20.

Indep. Claims	Extra Claims	Fee(\$)	Fee Paid (\$)
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_____ - 3 or HP= _____	x	_____	= _____
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HP = highest number of independent claims paid for, if greater than 3.

3. APPLICATION SIZE FEE

If the specification and drawings exceed 100 sheets of paper (excluding electronically filed sequence or computer listings under 37 CFR 1.52(e)), the application size fee due is \$250 (\$125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).

Total Sheets	Extra Sheets	Number of each additional 50 or fraction thereof	Fee (\$)	Fee Paid (\$)
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_____ - 100 = _____	/ 50 = _____	(round up to a whole number) x	= _____	
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4. OTHER FEE(S)

Non-English Specification, \$130 fee (no small entity discount)

Other (e.g., late filing surcharge) : Appeal brief fees under 37 CFR § 41.20(b)(2)

Fees Paid (\$)

500.00

SUBMITTED BY

Signature <i>Wei Zhou</i>	Registration No. (Attorney/Agent) 44,419	Telephone 408-731-5000
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This collection of information is required by 37 CFR 1.136. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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